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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/025,732	12/19/2001	William M. Pardridge	0180.0029	8416

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EXAMINER	
LAMBERTSON, DAVID A	
ART UNIT	**PAPER NUMBER**
1636	7

DATE MAILED: 09/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/025,732	PARDRIDGE, WILLIAM M.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *11-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,23 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-10, 23 and 24) in Paper No. 6 is acknowledged.

Claims 11-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 6.

Claims 1-26 are pending in the instant application. Claims 11-22 are withdrawn from consideration, leaving claims 1-10, 23 and 24 under consideration in the instant application.

Priority

Applicant's claim for domestic priority to US Application No. 09/557,349 under 35 U.S.C. 120 is acknowledged. However, the application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1-24 of this application. Specifically, there is no indication in the parent application of delivering therapeutic genes to ocular cells or a plurality of targeting agents for the blood retinal-barrier or ocular cell membrane. As such, applicant is granted priority only to the filing date of the instant application, December 19, 2001.

Information Disclosure Statement

The information disclosure statement filed March 7, 2002 as Paper No. 3 has been considered, and a signed and initialed copy of the form PTO-1449 has been attached to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 23 and 24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), and the most relevant factors are indicated below:

Nature of the invention. The nature of the invention is a receptor-specific liposome for the delivery of a therapeutic gene to ocular cells. The asserted use for the liposome is in a gene therapy method. This is evidenced by the disclosure in the specification of using the liposome in therapeutic approaches and the fact that the gene to be delivered is indicated as "therapeutic" in the claim language. Claim 23 further indicates that the claimed composition is pharmaceutical which necessarily implies that the composition is to be used for therapeutic purposes. As such, the nature of the invention is a molecule to be used in gene therapy. In order to meet the

enablement standards, the specification must enable the use of the claimed invention for gene therapy purposes.

Scope of the invention. The scope of the invention is very broad, encompassing the use of any "therapeutic" gene for the gene therapy of any disorder associated with ocular cells/the eye. There is no indication in the instant specification as to what genes can be used as therapeutic agents, or for what disorders any individual gene can be used.

State of the art. The state of the art regarding gene therapy, in general, is very poor. For instance, Verma *et al.* (*Nature* **389**: 239-242, 1997; see entire document; henceforth Verma) discuss many of the pitfalls associated with gene therapy approaches. Verma first indicates that there have been no success stories associated with gene therapy approaches (see for example page 239, left column, second paragraph). Indeed, even in what has been considered the most successful gene therapy approach, the treatment of SCID led by Alan Fischer, there are now reports of unpredictable results. As evidenced in a report by Check (*Nature* **421**: 678, 2003; see entire document; henceforth Check), the use of gene therapy to treat SCID has led to the appearance of cancer in a number patients as a result of the insertion of the therapeutic gene in an inappropriate spot in the patient's genome. Verma further indicates that there are many areas of uncertainty regarding the practice of gene therapy, including: determining how much of the therapeutic protein should be delivered, and what is referred to as the Achilles' heel of gene therapy-how to successfully target and deliver the therapeutic agent to a proper cell and sustain expression at a therapeutic level (see for example page 239, center and right columns). Verma indicates that many non-viral vectors, such as cationic lipids (i.e., a liposome), suffer from the inability to efficiently deliver and sustain expression of a gene, which is a conceptual hurdle that

is yet to be addressed (see for example page 329, right column, first full paragraph). The prior art provides no evidence that is contrary to this statement, indicating that these hurdles have been overcome.

As it regards gene therapy techniques which are specifically directed to disorders relating to the eye (i.e., ocular cells), the prior art is silent. There is no indication of what particular genes can be used to treat any given eye disorder, let alone what amounts of the particular gene must be used to generate a sufficient amount to elicit a therapeutic effect. Consequently, there is no successful demonstration of gene therapy for the eye. Thus, the skilled artisan could not rely on the prior art to use the claimed invention, and would be forced to rely on the instant specification in order to use the claimed invention.

Number of working examples and Guidance provided by applicant. The instant specification does not provide sufficient guidance to overcome the deficiencies in gene therapy that are present in the prior art. There is no indication of what genes can be used in a therapeutic treatment of the eye, or for what particular eye disorders any of the genes would be therapeutically effective. There is no indication as to what amounts of a given gene are necessary in order to achieve a therapeutic effect, a problem that was indicated by Verma to plague methods of gene therapy (see for example page 239, center column). There is no demonstration of a sustained expression level of the therapeutic gene in a manner that would elicit a therapeutic response, which Verma identifies as the Achilles' heel of gene therapy (see for example page 239, right column). Furthermore, there is no demonstration of an effective gene therapy use for the liposomes using an art-accepted model. The only guidance/example provided by the specification involves the transient expression of β-galactosidase, which is not a

therapeutic gene, in mouse ocular cells. Curiously, there is no demonstration that the expression of β-galactosidase is selective to ocular cells (i.e., receptor specific), therefore it is unknown if the liposomes are indeed receptor-specific for ocular cells when the liposome is administered in an organism. Furthermore, this model does not indicate that the expression was sustained for a therapeutically effective length of time. In short, the specification does not provide sufficient guidance that would allow the skilled artisan to use the claimed invention of a receptor-specific liposome for use in the delivery of therapeutic genes specifically to ocular cells.

Level of skill in the art. There is little-to-no success reported with regard to gene therapy. In fact, as stated above, a recent article by Check in Nature evaluated the situation concerning what had been regarded as the only successful gene therapy trial. In this article, it was demonstrated that a significant number of the participants had developed a specific type of cancer in response to the gene therapy treatment. Thus, the level of skill in the art of gene therapy is underdeveloped.

Unpredictability of the art and Amount of experimentation required. The art is highly unpredictable. In order to practice the invention, the skilled artisan would first have to empirically determine what genes could be used as therapeutic agents for the treatment of a particular disorder associated with ocular cells. Next, the skilled artisan would have to empirically determine the amount of a given gene or genes that would be need to be delivered to the afflicted cells in order to achieve a therapeutic effect. Then the skilled artisan would have to overcome the general deficiencies associated with gene therapy by developing an effective means to specifically deliver a therapeutic gene to an appropriate cell type, as well as a method of sustaining the expression of the therapeutic gene so as to achieve a therapeutic effect. Finally,

the skilled artisan would have to determine if the method actually could be performed successfully on an organism without causing another malady, such as the situation which arose from the gene therapy treatment of SCID. This represents an enormous amount of undue and unpredictable trial and error experimentation for the skilled artisan. Thus, the receptor-specific liposomes for the delivery of therapeutic genes to ocular cells are not enabled.

Claims 1-10, 23 and 24are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant claims a receptor-specific liposome comprising any therapeutic gene to be delivered to an ocular cell. The claims read on a broad genus of genes that must necessarily have a therapeutic effect on ocular cells.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicants were in possession of the claimed genus. In the instant case, the specification does not sufficiently describe a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics.

Applicant claims a therapeutic gene by function only, without any disclosed or known correlation between the elements and their function. The specification provides no teachings as to what genes would have a therapeutic effect on ocular cells. Similarly, there is no description of what particular 100 nucleotides would be sufficient to elicit a therapeutic effect. The specification only teaches a liposome for the delivery of marker genes, which are not considered therapeutic, to ocular cells. The skilled artisan cannot envision a sufficient number of therapeutic genes to be used in the receptor-specific liposomes of the instant invention from the instant specification, therefore the skilled artisan would not be able to envision the invention as claimed.

The prior art does not provide sufficient information on the subject to overcome the deficiencies of the instant specification. There is no description in the prior art that allows one to envision a representative number of therapeutic genes (or what 100 nucleotides of such a gene) that would be effective for treatment of disorders associated with ocular cells by disclosing either the structure-function features of such therapeutic genes or a representative number of such genes so that one of skill in the art could envision the claimed invention. Thus the skilled artisan cannot rely on the prior art to envision a sufficient number of embodiments of the instant invention to see that the applicant was in possession of the claimed genus.

Neither the specification of the instant application or the prior art teaches a structure-function relationship or by describing a representative number of therapeutic genes for delivery to ocular cells. As a result, the skilled artisan would not be able to envision the claimed invention by relying on the teachings of the prior art or the instant specification. Therefore applicant has not satisfied the written description requirement to show the skilled artisan that they were in possession of the claimed genus.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10, 23 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "sufficient amount" in claims 1 and 23 is a relative term which renders the claim indefinite. The term "sufficient amount" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The skilled artisan would not be clear on what amount of genetic information would be sufficient to encode a therapeutic gene. In fact, this would have to be determined empirically for each gene to be used in the liposome. Thus, the claim is indefinite because the skilled artisan would be unable to determine what amount of genetic information would need to be used to be in possession of the liposome as claimed.

Claim 1 recites the limitation "said nanocontainer" in lines 6 and 10 of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 3 recites a number of acronyms without indicating what the acronyms represent. It is unclear what is meant by the recitation of these acronyms, therefore the metes and bounds of the claim are not defined and the claim is indefinite.

Claims 3 and 10 are rejected under 35 USC 112, second paragraph, as being indefinite for failing to recite a proper Markush group. In order for the claims to be definite, they must recite

the proper Markush language, wherein the members of the Markush group are "selected from the group consisting of", followed by the listing of the members of the group. In addition, the conjunction "and" must follow the penultimate member of the group. Importantly, there should only be one conjunction recited in the body of the Markush group.

Claim 6 and 23 recite the limitation "said liposome" in the body of the claim. There is insufficient antecedent basis for this limitation in the claim. It would be remedial to indicate the language "said receptor-specific liposome" in order to indicate that the claim is not referring to some additional liposome.

Claim 9 recites the limitation "said blood-retinal targeting agent" in the first line of the claim. There is insufficient antecedent basis for this limitation in the claim. It would be remedial to indicate the language "said blood-retinal barrier targeting agent."

Conclusion

The following prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US Patent No. 6,372,250 (the issued patent from the parent application of the instant application) presents broad claims that encompass the specific claims of the instant invention (e.g., claims 22 and 23 of US Patent No. 6,372,250). However, the instant claims are not obvious or anticipated by the claims of US Patent No. 6,372,250 because the patent does not teach or suggest the use of targeting agents for ocular cells.

Allowable Subject Matter

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson
AU 1636

GERRY LEFFERS
PRIMARY EXAMINER